

UC San Diego

UC San Diego Previously Published Works

Title

Positive Surgical Margins in the 10 Most Common Solid Cancers.

Permalink

<https://escholarship.org/uc/item/4p48p7pw>

Journal

Scientific reports, 8(1)

ISSN

2045-2322

Authors

Orosco, Ryan K
Tapia, Viridiana J
Califano, Joseph A
et al.

Publication Date

2018-04-01

DOI


10.1038/s41598-018-23403-5

Peer reviewed

SCIENTIFIC REPORTS

OPEN

Positive Surgical Margins in the 10 Most Common Solid Cancers

Ryan K. Orosco¹ , Viridiana J. Tapia¹, Joseph A. Califano^{1,2,4}, Bryan Clary², Ezra E. W. Cohen^{4,5}, Christopher Kane^{4,6}, Scott M. Lippman^{4,5}, Karen Messer⁴, Alfredo Molinolo⁴, James D. Murphy⁷, John Pang¹, Assuntina Sacco^{4,5}, Kathryn R. Tringale¹, Anne Wallace^{2,4} & Quyen T. Nguyen^{1,2,3,4}

Received: 6 November 2017

Accepted: 5 March 2018

Published online: 09 April 2018

A positive surgical margin (PSM) following cancer resection oftentimes necessitates adjuvant treatments and carries significant financial and prognostic implications. We sought to compare PSM rates for the ten most common solid cancers in the United States, and to assess trends over time. Over 10 million patients were identified in the National Cancer Data Base from 1998–2012, and 6.5 million had surgical margin data. PSM rates were compared between two time periods, 1998–2002 and 2008–2012. PSM was positively correlated with tumor category and grade. Ovarian and prostate cancers had the highest PSM prevalence in women and men, respectively. The highest PSM rates for cancers affecting both genders were seen for oral cavity tumors. PSM rates for breast cancer and lung and bronchus cancer in both men and women declined over the study period. PSM increases were seen for bladder, colon and rectum, and kidney and renal pelvis cancers. This large-scale analysis appraises the magnitude of PSM in the United States in order to focus future efforts on improving oncologic surgical care with the goal of optimizing value and improving patient outcomes.

One in four deaths in the United States (US) is due to cancer¹. Treatment modalities vary considerably depending on stage and location, however surgical excision is an integral part of treatment for most solid tumors. The goal of surgical resection is the eradication of cancer—both gross and microscopic. A positive surgical margin (PSM) occurs when this ideal is not achieved, and cancer cells are present at the edge of the resection specimen. The cancer biology, responses to neo-adjuvant and adjuvant therapies, and treatment paradigm differs across tumor types. Similarly, the impact that a PSM has on prognosis and treatment decisions depends on tumor type. For example, the 2017 National Comprehensive Cancer Network (NCCN) guidelines for kidney and ovarian cancer do not include surgical margins, but margins are mentioned 16 times in the oral cavity cancer guidelines. In general, PSMs warrant additional (adjuvant) treatments, which confer significant increased costs and burden to the patient and healthcare system².

To broadly characterize the scope of PSMs in surgical cancer care, we used today's largest oncology database, the National Cancer Data Base (NCDB), to evaluate PSM prevalence in the ten most common solid organ cancers in the US.

Methods

The ten most common solid organ cancers in the US are: prostate, breast, lung and bronchus, colon and rectal, urinary bladder, thyroid, kidney and renal pelvis, uterine corpus, oral cavity, ovarian³. We included NCDB data (1998–2012) of patients with these cancers as their only malignancy ($n = 10,400,589$ Supplemental Table 1), and excluded patients: treated without surgery ($n = 3,028,552$), who underwent local tumor destruction ($n = 98,450$), with unknown surgery status ($n = 62,071$). Of the remaining 7,211,516 patients who underwent surgical resection of their cancer, surgical margin information was available for 6,495,889 (90.1%, Supplemental Table 1).

We examined the NCDB variable “margin status”, which represents presence or absence of tumor following primary resection. PSM was defined as “microscopic residual tumor” ($n = 311,635$), “macroscopic residual tumor” ($n = 48,871$), or “residual tumor, not otherwise specified (NOS)” ($n = 214,675$). Negative margins were defined as “no residual tumor” ($n = 5,920,708$). For patients undergoing multiple sequential surgeries, the NCDB

¹Division of Otolaryngology, Head and Neck Surgery, University of California, San Diego, CA, USA. ²Department of Surgery, University of California, San Diego, CA, USA. ³Department of Pharmacology, University of California, San Diego, CA, USA. ⁴Moore's Cancer Center, University of California, San Diego, CA, USA. ⁵Department of Medicine, Division of Hematology-Oncology, University of California, San Diego, CA, USA. ⁶Department of Urology, University of California, San Diego, CA, USA. ⁷Department of Radiation Medicine and Applied Sciences, San Diego, CA, USA. Correspondence and requests for materials should be addressed to Q.T.N. (email: q1nguyen@ucsd.edu)

only reports the margin status of the final procedure, but does not specify which patients had multiple surgeries. Tumor (T) categories in the NCDB are based on the American Joint Committee on Cancer (AJCC) 6th and 7th editions.

PSM rates were determined for each cancer site by year, T category, gender, age group, and race. To assess PSM change over the study period, we compared PSM rates for the last 5 years (2008–2012) to the first 5 years (1998–2002), using the two-proportion z-test with pooled standard error. Additionally, we conducted a multivariable logistic regression to investigate the adjusted effect of these time periods on PSM. Patient-related covariates included: gender, age, race/ethnicity, income, Charlson-Deyo⁴ comorbidity index (CI), and insurance type. Median household income, estimated by correlating postal code time of diagnosis with American Community Survey data, 2008–2012 and adjusted for inflation, was categorized by quartile (1st quartile < \$38,000; 2nd \$38,000–47,999; 3rd \$48,000–62,999; 4th > \$63,000). Tumor-related covariates included: tumor stage (T-stage) and histologic grade (American Joint Committee on Cancer (AJCC) seventh edition guidelines for pathologic staging⁵). Healthcare system covariates included: hospital tumor-specific case volume, facility type, and geographic location. Hospital tumor-specific volume was calculated using average number of cases reported to the NCDB per year (low volume < 25th percentile, high volume > 75th percentile). Facility type was based on CoC accreditation criteria. Statistical analyses were performed using STATA, version 13 (Stata, StataCorp LP, College Station, Texas).

The prognostic implications of PSM and accompanying adjuvant treatment considerations and costs were summarized. Adjuvant treatment recommendations were obtained from National Comprehensive Cancer Network (NCCN). This study was approved by the UCSD Institutional Review Board (protocol #150107). All methods were performed in accordance with relevant guidelines and regulations.

Disclosure. The American College of Surgeons and the CoC have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Results and Discussion

Most patients were women (66.2%) and White (76.04%). There were 2,530,565 breast, 761,637 prostate, 241,791 bladder, 1,218,834 colon and rectum, 314,459 thyroid, 120,826 oral cavity, 462,282 lung and bronchus, 361,240 kidney and renal pelvis, 391,997 uterine, and 92,058 ovarian cases (Supplemental Table 1). There were 9.38% *in situ*, 43.25% T1, 20.04% T2, 13.74% T3, and 3.99% T4 cases. For each cancer site, PSM increased with higher tumor category and grade (Table 1).

PSM trends over time. Unadjusted PSM rates for breast, and lung and bronchus cancer in both men and women declined over the period of the study (Fig. 1A,B, Table 1). In contrast, PSM rates for bladder, colon and rectum, and kidney and renal pelvis increased for both genders. Ovarian cancer PSM rates decreased over time (Fig. 1A,B, Table 1).

Multivariable logistic regression analysis showed that patients treated in the second seven years (2006–2012) were more likely to have PSM for bladder (OR 1.09, $p = 0.007$) and kidney (OR 1.29, $p < 0.0001$) tumors, and less likely to have PSM for breast (OR 0.78, $p < 0.0001$), lung (OR 0.93, $p = 0.002$), and prostate (OR 0.96, $p = 0.045$) tumors (1998–2005) (Table 1). This means that a patient having surgery between 2006 and 2012 had a 22% lower chance of having a PSM than a patient treated during the 1998–2002 time period.

Clinical and financial impact PSM. The prognostic implications of PSM and accompanying adjuvant treatment considerations and costs are summarized in Table 2 for eight of the tumor sites—breast, prostate, bladder, colon and rectum, thyroid, oral cavity, lung and bronchus, uterine. The NCCN treatment guidelines for kidney and renal pelvis and ovarian cancers do not account for PSM, but a summary of corresponding PSM implications is provided in the manuscript text.

PSM for cancers affecting both genders. The highest PSM rates for cancers affecting both genders were oral cavity (12.75%), followed by thyroid cancers (11.52%). The greatest gender-specific difference in PSM rate was seen in bladder cancer (11.58% in women vs. 8.96% in men).

Breast cancer. Lumpectomy and mastectomy PSM rates were 6.58% and 5.30%, respectively (Table 1). PSM rates for lumpectomy is significantly lower than the reported national estimate of 22.9%⁵. This is likely due to NCDB's practice of reporting final PSM, even if a patient has had multiple sequential procedures. Breast cancer patients may undergo multiple sequential lumpectomies, followed by mastectomy for persistent PSM.

Following mastectomy, PSM in node-negative disease is associated with an increased locoregional recurrence (LRR) and decreased disease-specific survival (DSS) (Table 2)⁶. In a meta-analysis, Moran *et al.* found that patients with close or PSM had 2-times greater odds of developing tumor recurrence than patients with negative margins⁷.

NCCN guidelines² for patients with PSM is stratified by stage (Table 2). Patients with early-stage tumors are recommended to undergo re-excision, mastectomy; or for focal PSM without extensive intraductal component, a high chest wall irradiation boost. One in four women who undergo an attempt at breast-conserving therapy have positive or unclear margins and go on to have re-excision^{5,8}. For patients with PSM after mastectomy, the NCCN recommends radiation to the chest wall, infraclavicular and supraclavicular regions, and potentially to the internal mammary nodes and any other part of the axillary bed at risk. These additional procedures confer increased discomfort and stress, increased risk of complications, potentially compromised aesthetic outcomes, and increased health care costs for both the patient and the healthcare system^{7,9–11}.

	BREAST (LUMP, MAST, TOTAL)			PROSTATE	BLADDER	COLON & RECTUM	THYROID	ORAL CAVITY	LUNG & BRONCHUS	KIDNEY & RENAL PELVIS	UTERINE	OVARIAN	TOTAL
Number of Cases (n)	1,479,230	1,051,335	2,530,565	761,637	241,791	1,218,834	314,459	120,826	462,482	361,240	391,997	92,058	6,495,889
Number of PSM Cases	97,335	55,746	153,081	160,194	23,317	83,241	36,230	15,411	33,861	20,691	16,938	32,217	575,181
Overall PSM Rate (%)	6.58	5.30	6.05	21.03	9.64	6.83	11.52	12.75	7.32	5.73	4.32	35.00	8.85%
Gender													
Men	8.30	4.47	5.53	21.03	8.96	6.71	13.24	12.65	8.00	6.04	N/A	N/A	7.73% (109,572) ^a
Women	6.57	5.32	6.05	N/A	11.58	6.95	10.99	12.92	6.64	5.23	4.32	35.00	6.69% (256,260) ^a
Race													
White	6.32	5.08	5.81	20.60	9.31	6.66	10.90	12.30	7.15	5.80	3.86	35.67	8.60% (424,725)
Black/AA	7.93	6.53	7.32	23.19	14.19	7.43	8.76	18.62	8.53	4.99	7.90	33.47	10.04% (58,393)
Other	7.28	5.68	6.57	22.21	9.20	7.12	15.32	13.62	7.46	5.82	4.78	27.81	9.34% (19,087)
Latino/Hispanic	7.07	5.53	6.41	21.65	10.28	7.34	14.53	13.15	7.83	5.84	4.66	33.86	9.47% (72,976)
Age													
<40	8.62	6.32	7.33	17.17	6.94	9.78	10.43	10.56	9.56	4.20	3.52	15.64	8.42% (28,867)
41–80	6.15	5.12	5.73	21.08	8.78	6.75	11.60	12.70	7.25	5.72	4.16	36.49	8.89% (494,280)
>81	10.18	6.14	8.45	17.07	13.41	6.68	23.78	14.09	7.79	7.10	6.78	42.76	8.74% (52,034)
T-category													
In Situ	5.67	3.19	4.89	0.00	3.30	1.41	0.00	9.33	4.80	3.26	0.58	N/A	4.39% (26,766)
T1	5.63	3.74	4.99	19.02	6.24	2.74	5.21	7.85	3.05	2.87	1.00	3.94	5.96% (167,291)
T2	9.13	5.27	6.97	19.58	17.37	1.92	8.26	14.92	6.77	2.73	5.87	27.78	8.50% (110,683)
T3	20.11	9.55	11.05	45.95	24.07	5.61	24.79	20.32	19.57	14.17	25.70	58.25	11.26% (100,539)
T4	37.60	18.58	20.89	65.54	40.33	27.05	50.76	25.18	27.13	42.04	51.89	N/A	29.96% (77,740)
Grade													
Well Differentiated	5.19	4.14	4.85	9.64	2.41	4.68	9.10	9.70	4.45	2.73	0.02	10.35	4.47% (44,669)
Mod Differentiated	6.66	5.23	6.07	15.99	4.75	5.82	19.52	13.81	6.32	3.61	2.53	25.98	7.51% (195,187)
Poorly Differentiated	7.21	5.94	6.59	27.31	14.47	12.47	32.77	18.61	8.71	8.44	10.77	45.22	13.11% (229,211)
Undifferentiated	8.45	6.95	7.76	31.51	16.26	15.54	61.89	20.57	9.91	16.28	15.58	48.31	16.46% (24,681)
Change over study period													
Men			−3.22** (−3.96:−2.47)	−0.213 (−0.44:0.02)	2.95** (2.62:3.27)	2.41** (2.25:2.56)	−0.775* (−1.43:−0.12)	−0.252 (−0.83:0.33)	−0.374* (−0.65:−0.10)	1.44** (1.18–1.70)	NA	NA	
Women			−3.63** (−3.70:−3.55)	NA	3.72** (3.11:4.33)	2.38** (2.23:2.54)	0.528* (−0.12:0.19)	−1.15** (−1.89:−0.41)	−0.74** (−0.99:−0.49)	1.19** (0.88:1.49)	0.481** (0.33–0.64)	−4.59** (−5.2:−3.97)	

Table 1. Prevalence of PSM for individual tumor sites as a function of gender, race, age, tumor category, tumor grade. Analysis of PSM change over study period comparing unadjusted rate from the last 5 years of the study period 2008–2012 to the first 5 years of the study period (1998–2002). a. Only tumors occurring in both genders are included here. b. Numbers given are percents unless otherwise indicated. * $p < 0.05$; ** $p < 0.001$, Not applicable (NA).

Oral Cavity cancer. The PSM rate for oral cavity cancer was 12.75% (Table 1)—the highest overall PSM rate for tumors affecting both genders. This finding is consistent with prior figures, although it is important to note that previously reports on PSM rates ranged widely (range 1–22%) and with some exceptions¹², were derived primarily from single-institution studies, and often included extra-oral sites^{13–16}.

The prognostic implication of PSM in oral cavity cancer is significant. PSMs are independently associated with increased risk of LRR and decreased overall survival (OS) (Table 2)^{13–16}. Sutton *et al.* reported a relative risk of death of 11.61 ($p = 0.0013$) for patients with PSM and 2.66 ($p = 0.02$) for patients with close margins, compared to those with negative margins¹⁷.

NCCN² recommends that oral cavity cancer patients with PSM receive adjuvant therapy (Table 2), which is stratified based on stage. Early-stage patients (stage I–II) should undergo re-resection to obtain negative margins when feasible; otherwise they should receive radiation, or radiation with chemotherapy (for T2 tumors only). Locally advanced stage patients (stage III–IV, non-metastatic) should receive radiation with chemotherapy

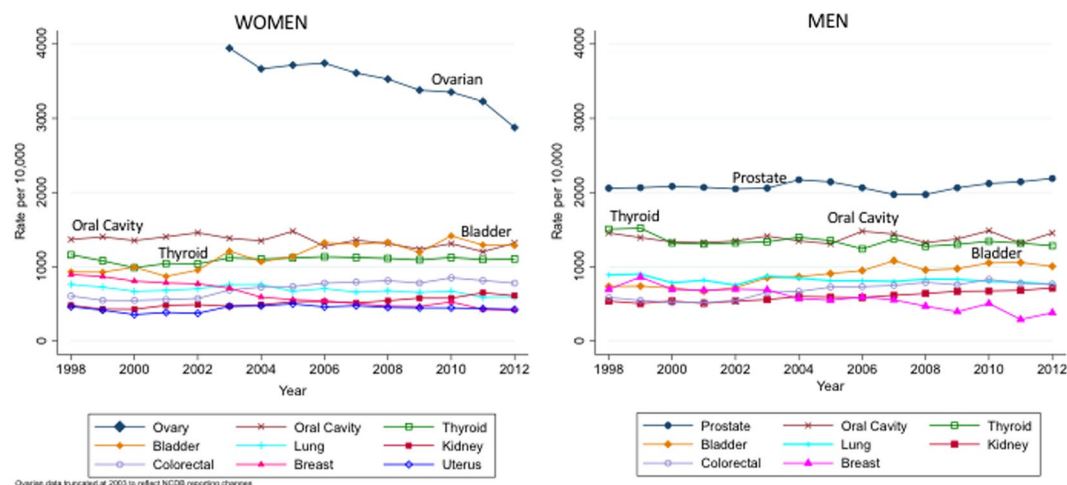


Figure 1. Positive surgical margin (PSM) prevalence (reported as rate per 10,000 patients) for each cancer in women (A) and men (B) as a function of time.

(category 1 recommendation), re-resection, or radiation alone. The need for adjuvant therapy—whether it be surgery, radiation, or radiation with chemotherapy—confers increased healthcare costs (Table 2) and subjects the patient to additional toxicities which can adversely impact quality of life¹⁸.

Bladder. PSM rate for bladder cancer was 9.64%, with women having higher PSM (11.58%) compared to men (8.56%) (Table 1). Our study is limited by NCCN coding which does not differentiate transurethral resection of bladder tumors from radical cystectomies. Thus, the PSM rates reported here reflect a combination of these two different procedures. Published PSM rates are divided based on presence or absence of muscle invasion, where non-muscle invasive refers to Ta, CIS or T1 tumor category, and muscle-invasive refers to all other tumor categories². Based on a comprehensive literature review, Divrik *et al.* reported that the rates of residual tumor in non-muscle invasive bladder cancer after a transurethral resection of the bladder ranged from 28% to 74%¹⁹. In contrast, our study finds that non-muscle invasive tumors (Ta, CIS, T1) had a PSM rate of 6.24% at radical cystectomy. For muscle-invasive bladder cancer, a 2010 multi-site study of 513 patients reported a 6.8% rate of PSM²⁰, which is much lower than our PSM rates ranging from 17.37–40.33% (T-categories 2–4). This variability is likely due in part to differences in the underlying characteristics of the study populations, and to the inclusion of low and high volume centers in the NCCN.

Incomplete resection of bladder tumor, irrespective of muscle invasion has been associated with unfavorable prognosis (Table 2). Studies of PSM in patients with non-muscle invasive cancer showed decreased recurrence-free survival. Dotan *et al.* examined the importance of margins in patients undergoing radical cystectomy for muscle-invasive bladder cancer. They demonstrated that PSM had a profoundly negative impact on cancer specific survival, which decreased from 72% to 32% at 5 years. They also demonstrated that patients with PSM had a 3.5-fold increased risk (21% vs 6%) of local recurrence at 5 years, which is almost uniformly fatal. On multivariate analysis, PSM was an independent predictor of death from cancer²¹. The higher PSM rate for women may be due to the increased technical challenge of radical cystectomy and anterior exenteration in women which requires anterior vaginal dissection and hysterectomy and salpingo-oophorectomy.

NCCN² recommends adjuvant radiotherapy or chemotherapy for patients with stage II margin positive disease (Table 2). Radical cystectomy is relatively contraindicated in patients with positive urethral margin, and chemoradiation is preferred²². Late stage bladder cancer requires higher radiotherapy boost².

Colon and Rectum. The total PSM rate for colon and rectal cancer was 6.83%. Higher PSM rates correlated with higher T-category (Table 1), a finding consistent with prior reports²³. For colon cancer, PSM is a poor prognostic feature for T2 and T3 tumors²⁴. For rectal cancer, PSMs are considered a high-risk pathologic feature. In a Dutch study on rectal cancer, patients with PSM had a local recurrence rate of 22%, compared with 4% of those with negative margins²⁵. Lin *et al.* also showed that when defining a PSM as less than 1 mm from the tumor, the rate of distant metastasis was 61.5%, compared with 15.2% for margins of >1 mm, making PSM a predictor for the development of distant metastasis²⁶ and decreased disease-free survival²⁷.

Based on NCCN guidelines², PSM in colon cancer may warrant larger resection, chemotherapy, and consideration for boost radiation (Table 2)^{2,27,28}. For rectal cancers, PSM may mean larger resection with or without chemoradiation, and intra-operative radiation therapy (IORT) may be considered for PSM especially in T4 and recurrent cancers.

Kidney and Renal Pelvis. In this study, the PSM rate for patients with kidney and renal pelvis cancer was 5.73% (Table 1). Our data are similar to the literature review by Borghesi *et al.* in 2013, reporting that the overall incidence of PSMs after nephron-sparing surgery (NSS) when performed electively is quite low, ranging from 0% to 7%²⁹. Comparable PSM rates have been reported between different surgical approaches: 0% to 7% in open partial

		BREAST	PROSTATE	BLADDER	COLON & RECTUM
Prognostic Implications for PSM		Increased LRR, decreased DSS	Increased risk of biochemical recurrence; no impact on cancer-specific mortality	Increased LRR, Decreased DSS	Increased LRR and DM, decreased DFS and OS
Adjuvant Treatment Recommendations for PSM based on NCCN Guidelines	Early Stage	PSM after lumpectomy: Re-excision OR Mastectomy OR Higher RT boost for focal PSM without extensive intraductal component	RT	Stage II (T2N0) RT, OR Chemo (if no neoadjuvant therapy) Stage II (T2N0) primary <i>urethra carcinoma</i> (males): Re-resection Or CRT (preferred) Or RT	Colon: larger resection, T3N0M0 chemo, and for any stage consider boost radiation
	Late Stage	PSM after mastectomy: Consider RT to chest wall +/- infraclavicular region +/- supraclavicular area +/- internal mammary nodes & any part of axillary bed at risk	RT	Stage III-IV (T3-4, N0-2) urothelial: Higher RT boost	Rectum: larger resection, T1Nx after trans-anal excision: Transabdominal resection +/- CRT or CRT, and intra-operative radiation therapy (IORT) may be considered for PSM especially in T4 and recurrent cancers
Cost of Adjuvant Treatment due to PSM	Surgery	Lumpectomy alone: \$70,520 Mastectomy alone: \$48,258 Mastectomy + Recon: \$88,089			
	Radiation	RT: \$8,600	RT: \$18,000		
	Chemotherapy			Chemo: \$16,416	Chemo: \$17,833
		THYROID	ORAL CAVITY	LUNG & BRONCHUS	UTERINE
Prognostic Implications for PSM		No impact	Increased LRR, Decreased OS	Decreased OS	Potential increase in LRR
Adjuvant Treatment Recommendations for PSM based on NCCN guidelines	Early Stage	PSM after partial thyroidectomy (papillary): Completion thyroidectomy	STAGE I-II: Re-resection OR RT OR CRT (T2 only)	STAGE IA: Re-resection (preferred) OR RT (category 2B) STAGE IB-IIA (node-negative): Re-resection (preferred) +/- chemo OR RT +/- chemo (chemo for stage IIA) STAGE IIA-B (node-positive): Re-resection+ chemo OR CRT	Vaginal brachytherapy and/or RT for stage I after extrafascial hysterectomy
	Late Stage		STAGE III-IV CRT (category 1) OR Re-resection OR RT	STAGE IIIA: CRT	T1, Nx rectal after trans-anal excision: Transabdominal resection +/- CRT OR CRT
Cost of Adjuvant Treatment due to PSM	Surgery	Surgery: \$5,617	Surgery: \$24,595	Surgery: \$15,034	
	Radiation		RT: \$21,300	RT: \$9,000	RT: \$9066 Brachytherapy: \$7233
	Chemotherapy		Chemo + RT: \$27,928		

Table 2. Summary of the prognostic implications, adjuvant treatment recommendations, and associated cost estimates of PSM for individual tumor sites: breast, prostate, bladder, colon and rectum, thyroid, oral cavity, lung and bronchus, uterine. *Unless otherwise specified, recommendations are category 2 A (uniform NCCN consensus that intervention is appropriate based on lower-level evidence). Kidney and Ovarian excluded as surgical margin status does not affect adjuvant therapy recommendations. **Cost for adjuvant treatment was obtained from published data in the United States (listed in U.S. dollars) where available. NCCN: National Comprehensive Cancer Network, PSM: positive surgical margin, RT: radiation therapy; chemo: chemotherapy, CRT: chemoradiation; LRR: locoregional recurrence rate, DSS: disease-specific survival, DM: distant metastasis, DFS: disease-specific survival, OS: overall survival.

nephrectomy, 0.7% to 4% in laparoscopic partial nephrectomy (LPN), and 0.7% to 4% in robot-assisted partial nephrectomy³⁰. Patients with an imperative indication for NSS seem to have a higher risk of PSM incidence (8.9–27.5%), likely due to the presence of larger tumors or unfavorable tumor location^{29,31}.

There is no clear consensus on clinical implications of PSM in these cancers. Some authors have found limited influence on long-term oncological outcomes³², whereas others showed that PSM increased the hazard ratio of recurrence and metastasis³³. Borghese *et al.* also reported that local recurrence seems to be more likely in patients with PSMs, especially in those with high-grade tumors²⁹. NCCN guidelines for kidney and renal pelvis cancers do not account for PSM².

Lung and Bronchus. We found an overall PSM rate of 7.32% for lung and bronchus cancers (Table 1), consistent with prior reports of PSM rates ranging from 6–7.8%^{34,35}. Interestingly, we found higher PSM rates in young patients (<40 years). Previous work has shown that among young patients, male sex, non-adenocarcinoma histology, black race, and main bronchial primary site are independent negative prognostic factors³⁶.

Surgical resection plays a critical role in the treatment of lung cancer³⁷, often providing the only potentially curative treatment for non-small cell lung cancer (NSCLC). However, clear surgical margins are difficult to obtain due to the limited amount of resectable tissue. Furthermore, the presence of occult micro-metastases are not uncommon³⁸. Five-year OS following surgery for patients with stage I–III NSCLC is less than 50%^{39,40} and 30–55% of NSCLC patients who undergo curative resection develop recurrence and die of their disease³⁸. PSMs are associated with poor prognosis, significantly impact survival irrespective of stage³⁷ and approximately halve the five-year survival rate^{41–43}. Moving forward, tumor markers and intraoperative visualization may help better establish early- versus advanced-stage disease^{44–46}.

NCCN (Table 2)² recommends adjuvant treatment for PSMs based on stage¹¹. Re-resection is typically preferred for early-stages with the option of concurrent chemotherapy, and alternatively, radiotherapy. For later stages, chemoradiotherapy is recommended as the preferred treatment in cases of PSM, which confers additional costs (Table 2).

Thyroid. Thyroid had one of the highest PSM rates (11.52%) of all cancers in this study (Table 1). This is comparable to a report of 10% PSMs from a retrospective study of patients with differentiated thyroid cancer⁴⁷. Over the study period, the prevalence of PSM rates decreased in men, yet increased in women. This is interesting, particularly given less aggressive histologic subtypes are more common in women⁴⁸. The highest PSM rate was seen in the elderly age group (23.78%).

Management of thyroid cancer is controversial due to the absence of high-level evidence regarding resection margins or adjuvant radiation therapy^{47,49}. A large NCDB study showed that total thyroidectomy results in lower recurrence rates and higher survival for papillary thyroid cancer, when compared to lobectomy⁵⁰. However, a more recent NCDB study did not observe a survival advantage with more extensive surgery⁵¹. Incomplete tumor resection has been recognized as one of the important poor prognostic factors in thyroid cancer patients who undergo total thyroidectomy⁵². American Thyroid Association has classified incomplete tumor resection as group at high-risk of recurrence⁵³. In patients with non-invasive thyroid cancer, prior work has shown a significantly higher rate of early recurrence in the PSM group than the negative margin group—but all early recurrences were in regional lymph nodes of surgically non-dissected neck areas⁵². Disease-free survival has been shown to be impacted by PSM and extension of the tumor beyond the thyroid capsule⁵⁴, prompting surgeons to weigh the possibility of impacting the functionality and quality of life of the patient against the aggressive surgical approaches that are more likely to completely clear tumor burden^{55,56}.

NCCN² recommends completion thyroidectomy for well-differentiated thyroid cancer with PSM (Table 2)⁵⁷.

PSM for cancers affecting males only. **Prostate.** Prostate had the highest PSM rate (21.03%) of any cancer in men (Table 1). Reported PSM incidence for radical prostatectomy varies widely (4% to greater than 48%)^{58,59}. Yossepowitch *et al.* reported an average PSM rate in contemporary robot-assisted laparoscopic radical prostatectomy series of 15% (range 6.5–32%)⁶⁰. Our multivariable analysis showed a notable prostate cancer PSM decrease between 2007–2012, which may be a result of more cancers being detected at earlier stages due to heightened PSA screening. Movement away from PSA screening since 2012 may reverse this trend.

Generally, urologic surgeons prioritize the preservation of as much of the neurovascular bundle as possible to prevent urinary incontinence and erectile dysfunction, thus precluding the execution of a wide surgical excision of periprostatic tissue and risking the occurrence of PSM⁶¹. Prostate cancer patients of advanced age were less likely to have PSM, indicating that most elderly patients likely underwent radical prostatectomy without nerve sparing, perhaps due to poorer pretreatment sexual function.

The clinical impact of PSM after radical prostatectomy has been studied extensively and there is a consensus that PSM is associated with a significantly increased risk of biochemical recurrence^{62–64}. However, prior work has shown that neither single PSMs, nor multiple PSMs, post-radical prostatectomy were independent risk factors for metastases, castration-resistant prostate cancer, cancer-specific death, or all cause death in a cohort of patients who received early salvage radiotherapy upon biochemical recurrence⁶⁴. While more aggressive tumor characteristics have been identified as strong determinants for PSM, margin status was not an independent prognostic factor for survival⁶⁵.

Per NCCN², radiation therapy, either as adjuvant or early salvage therapy is indicated for PSMs to reduce the risk of biochemical recurrence (Table 2). The rapid adoption of new technologies for more targeted radiation such as intensity-modulated radiation has contributed to the increasing costs of radiation for prostate cancer, which is increasing faster than the costs of care for cardiovascular and pulmonary conditions⁶⁶.

PSM for cancers affecting females only. **Ovarian.** Ovarian had the highest PSM rate among cancers affecting women (35.0%) and showed a significant decline over the study period (Table 1, Fig. 1A).

Patients with ovarian cancer are generally treated with a combination of surgery and adjuvant chemotherapy. As mentioned previously, PSM is not part of the treatment paradigm for ovarian cancers², as the surgical approach is focused on cytoreduction. Patients with newly-diagnosed, advanced ovarian cancer should have maximal surgical debulking to achieve minimal residual disease (residual implants < 1 cm).

Secondary debulking surgeries are potentially beneficial for patients who have an isolated relapse after a lengthy disease-free interval⁶⁷. Studies have demonstrated that the volume of post-operatively residual disease inversely correlates with survival^{68–70}. Interestingly, we found that PSM rates decreased over the study period on

univariable analysis. We hypothesize that this may be due to increased attention to the importance of reducing residual disease in cytoreductive surgeries⁷¹. However, this decrease was not noted in the multivariable logistic regression, likely due other confounding patient/tumor/institutional factors.

Ovarian had the highest PSM rate among cancers affecting women (35.0%). PSM for these cancers showed a significant decline over the study period on univariate, but not multivariate, analysis (Table 1, Fig. 1A). We hypothesize that this decline may be due to increased attention to the importance of reducing residual disease in cytoreductive surgeries⁷⁰. However, the interpretation of PSM for this tumor type is unclear, and the implications of these ovarian NCDB data are limited. Other data sources with detailed cytoreductive information would contribute to the surgical literature in a more relevant way.

Uterine. Uterine had the lowest PSM rate among cancers affecting women (4.32%). Elderly women, and patients with high stage and grade of uterine cancer, had higher PSM rates. PSM rates significantly increased throughout the study period (Table 1). To our knowledge, population-level PSM rates have not been reported in uterine cancer. The 26th Annual Report of the International Federation of Gynecology and Obstetrics (FIGO) states that 83% of endometrial cancer patients are diagnosed and treated at early-stage (FIGO I and II)^{72,73}. Surgery is the cornerstone of managing these early-stage patients.

The impact of PSM on clinical endpoints in endometrial cancer has been studied extensively. One study in Stage II endometrial cancer with extension into the cervix suggested that minimizing PSM at the cervical junction with an extended (radical) hysterectomy and removal of parametria should reduce LRR and possibly improve survival⁷⁴. Additional work has shown an increased rate of local recurrence in patients undergoing extra-fascial hysterectomy as opposed to radical hysterectomy, presumably due to the reduction in positive surgical margins at the cervical junction⁷⁵. Most recently, an NCDB study showed increased hazards for death among patients with PSMs⁷⁶.

NCCN² recommends adjuvant radiation⁷⁷ for PSM after extrafascial hysterectomy in the case of invasive cervical component (Table 2).

Limitations. This study is based on information from a national database, and lacks details about the criteria used to categorize margin status. There is no pathology information about how many millimeters the tumor was from the specimen edge. Additionally, the data set lacks information on number of resections or sequential procedures. Accordingly, the PSM prevalence reported here likely underestimates true PSM rates at the time of initial surgical resection.

Conclusion

This work serves to define the magnitude of PSM as a surgical challenge in the most common solid cancers in the US. Treatment algorithms vary considerably depending on cancer site and stage, but surgical excision remains axiomatic. A PSM commonly translates into worse prognosis and additional burden to patients and the health-care system by necessitating adjuvant therapies. Our findings may be helpful to prioritize efforts aimed at mitigating PSM, thereby optimizing value and improving patient outcomes.

References

1. Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2016. *CA Cancer J Clin* **66**, 7–30, <https://doi.org/10.3322/caac.21332> (2016).
2. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology. Version 2.2016*, https://www.nccn.org/professionals/physician_gls/f_guidelines.asp-site (2016).
3. Siegel, R., Naishadham, D. & Jemal, A. Cancer statistics, 2012. *CA Cancer J Clin* **62**, 10–29, <https://doi.org/10.3322/caac.20138> (2012).
4. Deyo, R. A., Cherkin, D. C. & Ciol, M. A. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* **45**, 613–619 (1992).
5. McCahill, L. E. *et al.* Variability in reexcision following breast conservation surgery. *JAMA* **307**, 467–475, <https://doi.org/10.1001/jama.2012.43> (2012).
6. Meric, F. *et al.* Positive surgical margins and ipsilateral breast tumor recurrence predict disease-specific survival after breast-conserving therapy. *Cancer* **97**, 926–933, <https://doi.org/10.1002/cncr.11222> (2003).
7. Moran, M. S. *et al.* Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Int J Radiat Oncol Biol Phys* **88**, 553–564, <https://doi.org/10.1016/j.ijrobp.2013.11.012> (2014).
8. Morrow, M. *et al.* Surgeon recommendations and receipt of mastectomy for treatment of breast cancer. *JAMA* **302**, 1551–1556, <https://doi.org/10.1001/jama.2009.1450> (2009).
9. King, T. A. *et al.* Clinical management factors contribute to the decision for contralateral prophylactic mastectomy. *J Clin Oncol* **29**, 2158–2164, <https://doi.org/10.1200/JCO.2010.29.4041> (2011).
10. Smith, B. D. *et al.* Cost and Complications of Local Therapies for Early-Stage Breast Cancer. *J Natl Cancer Inst* **109**, <https://doi.org/10.1093/jnci/djw178> (2017).
11. Paravati, A. J. *et al.* Variation in the Cost of Radiation Therapy Among Medicare Patients With Cancer. *J Oncol Pract* **11**, 403–409, <https://doi.org/10.1200/JOP.2015.005694> (2015).
12. Luryi, A. L. *et al.* Positive surgical margins in early stage oral cavity cancer: an analysis of 20,602 cases. *Otolaryngol Head Neck Surg* **151**, 984–990, <https://doi.org/10.1177/0194599814551718> (2014).
13. Binahmed, A., Nason, R. W. & Abdoh, A. A. The clinical significance of the positive surgical margin in oral cancer. *Oral Oncol* **43**, 780–784, <https://doi.org/10.1016/j.oraloncology.2006.10.001> (2007).
14. Chen, T. Y., Emrich, L. J. & Driscoll, D. L. The clinical significance of pathological findings in surgically resected margins of the primary tumor in head and neck carcinoma. *Int J Radiat Oncol Biol Phys* **13**, 833–837 (1987).
15. Jacobs, J. R. *et al.* Implications of positive surgical margins. *Laryngoscope* **103**, 64–68, <https://doi.org/10.1288/00005537-199301000-00012> (1993).
16. Jones, A. S. Prognosis in mouth cancer: tumour factors. *Eur J Cancer B Oral Oncol* **30B**, 8–15 (1994).
17. Sutton, D. N., Brown, J. S., Rogers, S. N., Vaughan, E. D. & Woolgar, J. A. The prognostic implications of the surgical margin in oral squamous cell carcinoma. *Int J Oral Maxillofac Surg* **32**, 30–34, <https://doi.org/10.1054/ijom.2002.0313> (2003).
18. Acevedo, J. R. *et al.* Cost-Effectiveness Analysis of Elective Neck Dissection in Patients With Clinically Node-Negative Oral Cavity Cancer. *J Clin Oncol* <https://doi.org/10.1200/JCO.2016.68.4563> (2016).

19. Divrik, R. T., Sahin, A. F., Yildirim, U., Altok, M. & Zorlu, F. Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: a prospective randomised clinical trial. *Eur Urol* **58**, 185–190, <https://doi.org/10.1016/j.eururo.2010.03.007> (2010).
20. Hellenthal, N. J. *et al.* Surgical margin status after robot assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. *J Urol* **184**, 87–91, <https://doi.org/10.1016/j.juro.2010.03.037> (2010).
21. Dotan, Z. A. *et al.* Positive surgical margins in soft tissue following radical cystectomy for bladder cancer and cancer specific survival. *J Urol* **178**, 2308–2312; discussion 2313 <https://doi.org/10.1016/j.juro.2007.08.023> (2007).
22. Stevenson, S. M. *et al.* Cost-effectiveness of neoadjuvant chemotherapy before radical cystectomy for muscle-invasive bladder cancer. *Urol Oncol* **32**, 1172–1177, <https://doi.org/10.1016/j.urolonc.2014.05.001> (2014).
23. Kanters, A. *et al.* Colorectal cancer: Quality of surgical care in Michigan. *Am J Surg* **213**, 548–552, <https://doi.org/10.1016/j.amjsurg.2016.11.038> (2017).
24. Chu, Q. D., Zhou, M., Medeiros, K. & Peddi, P. Positive surgical margins contribute to the survival paradox between patients with stage IIB/C (T4N0) and stage IIIA (T1–2N1, T1N2a) colon cancer. *Surgery* **160**, 1333–1343, <https://doi.org/10.1016/j.surg.2016.05.028> (2016).
25. Peeters, K. C. *et al.* The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* **246**, 693–701, <https://doi.org/10.1097/01.sla.0000257358.56863.ce> (2007).
26. Lin, H. H. *et al.* Circumferential margin plays an independent impact on the outcome of rectal cancer patients receiving curative total mesorectal excision. *Am J Surg* **206**, 771–777, <https://doi.org/10.1016/j.amjsurg.2013.03.009> (2013).
27. Sasikumar, A., Bhan, C., Jenkins, J. T., Antoniou, A. & Murphy, J. Systematic Review of Pelvic Exenteration With En Bloc Sacrectomy for Recurrent Rectal Adenocarcinoma: R0 Resection Predicts Disease-free Survival. *Dis Colon Rectum* **60**, 346–352, <https://doi.org/10.1097/DCR.0000000000000737> (2017).
28. Schrag, D. The price tag on progress—chemotherapy for colorectal cancer. *N Engl J Med* **351**, 317–319, <https://doi.org/10.1056/NEJMp048143> (2004).
29. Borghesi, M., Brunocilla, E., Schiavina, R. & Martorana, G. Positive surgical margins after nephron-sparing surgery for renal cell carcinoma: incidence, clinical impact, and management. *Clin Genitourin Cancer* **11**, 5–9, <https://doi.org/10.1016/j.clgc.2012.09.010> (2013).
30. Marszalek, M. *et al.* Positive surgical margins after nephron-sparing surgery. *Eur Urol* **61**, 757–763, <https://doi.org/10.1016/j.eururo.2011.11.028> (2012).
31. Lee, D. J., Hruby, G., Benson, M. C. & McKiernan, J. M. Renal function and oncologic outcomes in nephron sparing surgery for renal masses in solitary kidneys. *World J Urol* **29**, 343–348, <https://doi.org/10.1007/s00345-010-0576-9> (2011).
32. Raz, O. *et al.* Positive surgical margins with renal cell carcinoma have a limited influence on long-term oncological outcomes of nephron sparing surgery. *Urology* **75**, 277–280, <https://doi.org/10.1016/j.urolgy.2009.06.110> (2010).
33. Khalifeh, A. *et al.* Positive surgical margins in robot-assisted partial nephrectomy: a multi-institutional analysis of oncologic outcomes (leave no tumor behind). *J Urol* **190**, 1674–1679, <https://doi.org/10.1016/j.juro.2013.05.110> (2013).
34. Little, A. G. *et al.* Patterns of surgical care of lung cancer patients. *Ann Thorac Surg* **80**, 2051–2056 discussion 2056 <https://doi.org/10.1016/j.athoracsur.2005.06.071> (2005).
35. Osarogiagbon, R. U. *et al.* Prognostic Value of National Comprehensive Cancer Network Lung Cancer Resection Quality Criteria. *Ann Thorac Surg* <https://doi.org/10.1016/j.athoracsur.2017.01.098> (2017).
36. Thomas, A., Chen, Y., Yu, T., Jakopovic, M. & Giaccone, G. Trends and Characteristics of Young Non-Small Cell Lung Cancer Patients in the United States. *Front Oncol* **5**, 113, <https://doi.org/10.3389/fonc.2015.00113> (2015).
37. Osarogiagbon, R. U. & D'Amico, T. A. Improving lung cancer outcomes by improving the quality of surgical care. *Transl Lung Cancer Res* **4**, 424–431, <https://doi.org/10.3978/j.issn.2218-6751.2015.08.01> (2015).
38. Uramoto, H. & Tanaka, F. Recurrence after surgery in patients with NSCLC. *Transl Lung Cancer Res* **3**, 242–249, <https://doi.org/10.3978/j.issn.2218-6751.2013.12.05> (2014).
39. Pfannschmidt, J., Muley, T., Bulzebruck, H., Hoffmann, H. & Dienemann, H. Prognostic assessment after surgical resection for non-small cell lung cancer: experiences in 2083 patients. *Lung Cancer* **55**, 371–377, <https://doi.org/10.1016/j.lungcan.2006.10.017> (2007).
40. Arriagada, R. *et al.* Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* **350**, 351–360, <https://doi.org/10.1056/NEJMoa031644> (2004).
41. Riquet, M. *et al.* Microscopic residual disease after resection for lung cancer: a multifaceted but poor factor of prognosis. *Ann Thorac Surg* **89**, 870–875, <https://doi.org/10.1016/j.athoracsur.2009.11.052> (2010).
42. Wind, J., Smit, E. J., Senan, S. & Eerenberg, J. P. Residual disease at the bronchial stump after curative resection for lung cancer. *Eur J Cardiothorac Surg* **32**, 29–34, <https://doi.org/10.1016/j.ejcts.2007.04.003> (2007).
43. Predina, J. D., Keating, J., Patel, N., Nims, S. & Singhal, S. Clinical implications of positive margins following non-small cell lung cancer surgery. *J Surg Oncol* **113**, 264–269, <https://doi.org/10.1002/jso.24130> (2016).
44. Orbay, H., Bean, J., Zhang, Y. & Cai, W. Intraoperative targeted optical imaging: a guide towards tumor-free margins in cancer surgery. *Curr Pharm Biotechnol* **14**, 733–742 (2013).
45. Bu, L., Shen, B. & Cheng, Z. Fluorescent imaging of cancerous tissues for targeted surgery. *Adv Drug Deliv Rev* **76**, 21–38, <https://doi.org/10.1016/j.addr.2014.07.008> (2014).
46. Woo, T. *et al.* Prognostic value of KRAS mutations and Ki-67 expression in stage I lung adenocarcinomas. *Lung Cancer* **65**, 355–362, <https://doi.org/10.1016/j.lungcan.2008.11.020> (2009).
47. Wang, L. Y. *et al.* Microscopic Positive Margins in Differentiated Thyroid Cancer Is Not an Independent Predictor of Local Failure. *Thyroid* **25**, 993–998, <https://doi.org/10.1089/thy.2015.0141> (2015).
48. Rahbari, R., Zhang, L. & Kebebew, E. Thyroid cancer gender disparity. *Future Oncol* **6**, 1771–1779, <https://doi.org/10.2217/fon.10.127> (2010).
49. Hartl, D. M. *et al.* Resection margins and prognosis in locally invasive thyroid cancer. *Head Neck* **36**, 1034–1038, <https://doi.org/10.1002/hed.23406> (2014).
50. Bilimoria, K. Y. *et al.* Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg* **246**, 375–381 discussion 381–374 <https://doi.org/10.1097/SLA.0b013e31814697d9> (2007).
51. Adam, M. A. *et al.* Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. *Ann Surg* **260**, 601–605 discussion 605–607 <https://doi.org/10.1097/SLA.0000000000000925> (2014).
52. Hong, C. M. *et al.* Prognostic implications of microscopic involvement of surgical resection margin in patients with differentiated papillary thyroid cancer after high-dose radioactive iodine ablation. *Ann Nucl Med* **26**, 311–318, <https://doi.org/10.1007/s12149-012-0574-7> (2012).
53. American Thyroid Association Guidelines Taskforce on Thyroid, N. *et al.* Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* **19**, 1167–1214, <https://doi.org/10.1089/thy.2009.0110> (2009).
54. Andersen, P. E., Kinsella, J., Loree, T. R., Shaha, A. R. & Shah, J. P. Differentiated carcinoma of the thyroid with extrathyroidal extension. *Am J Surg* **170**, 467–470 (1995).
55. Shah, J. P., Loree, T. R., Dharker, D. & Strong, E. W. Lobectomy versus total thyroidectomy for differentiated carcinoma of the thyroid: a matched-pair analysis. *Am J Surg* **166**, 331–335 (1993).

56. Sipos, J. A. & Mazzaferri, E. L. Thyroid cancer epidemiology and prognostic variables. *Clin Oncol (R Coll Radiol)* **22**, 395–404, <https://doi.org/10.1016/j.clon.2010.05.004> (2010).
57. Marino, M. *et al.* Costs of outpatient thyroid surgery from the University HealthSystem Consortium (UHC) database. *Otolaryngol Head Neck Surg* **150**, 762–769, <https://doi.org/10.1177/0194599814521583> (2014).
58. Cookson, M. S. & Chang, S. S. Margin control in open radical prostatectomy: what are the real outcomes? *Urol Oncol* **28**, 205–209, <https://doi.org/10.1016/j.urolonc.2009.09.019> (2010).
59. Silberstein, J. L. & Eastham, J. A. Significance and management of positive surgical margins at the time of radical prostatectomy. *Indian J Urol* **30**, 423–428, <https://doi.org/10.4103/0970-1591.134240> (2014).
60. Yossepowitch, O. *et al.* Positive surgical margins after radical prostatectomy: a systematic review and contemporary update. *Eur Urol* **65**, 303–313, <https://doi.org/10.1016/j.eururo.2013.07.039> (2014).
61. Preston, M. A. *et al.* The association between nerve sparing and a positive surgical margin during radical prostatectomy. *Urol Oncol* **33**(18), e11–16, <https://doi.org/10.1016/j.urolonc.2014.09.006> (2015).
62. Novara, G. *et al.* Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. *Eur Urol* **62**, 382–404, <https://doi.org/10.1016/j.eururo.2012.05.047> (2012).
63. Wright, J. L. *et al.* Positive surgical margins at radical prostatectomy predict prostate cancer specific mortality. *J Urol* **183**, 2213–2218, <https://doi.org/10.1016/j.juro.2010.02.017> (2010).
64. Mauermann, J. *et al.* The impact of solitary and multiple positive surgical margins on hard clinical end points in 1712 adjuvant treatment-naïve pT2–4 N0 radical prostatectomy patients. *Eur Urol* **64**, 19–25, <https://doi.org/10.1016/j.eururo.2012.08.002> (2013).
65. Retel, V. P. *et al.* Determinants and effects of positive surgical margins after prostatectomy on prostate cancer mortality: a population-based study. *BMC Urol* **14**, 86, <https://doi.org/10.1186/1471-2490-14-86> (2014).
66. Jacobs, B. L., Zhang, Y., Skolarus, T. A. & Hollenbeck, B. K. Growth of high-cost intensity-modulated radiotherapy for prostate cancer raises concerns about overuse. *Health Aff (Millwood)* **31**, 750–759, <https://doi.org/10.1377/hlthaff.2011.1062> (2012).
67. Schorge, J. O., McCann, C. & Del Carmen, M. G. Surgical debulking of ovarian cancer: what difference does it make? *Rev Obstet Gynecol* **3**, 111–117 (2010).
68. Bristow, R. E., Tomacruz, R. S., Armstrong, D. K., Trimble, E. L. & Montz, F. J. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* **20**, 1248–1259, <https://doi.org/10.1200/JCO.2002.20.5.1248> (2002).
69. Hoskins, W. J. *et al.* The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol* **170**, 974–979 discussion 979–980 (1994).
70. Chi, D. S. *et al.* What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? *Gynecol Oncol* **103**, 559–564, <https://doi.org/10.1016/j.ygyno.2006.03.051> (2006).
71. Winter, W. E. 3rd *et al.* Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* **26**, 83–89, <https://doi.org/10.1200/JCO.2007.13.1953> (2008).
72. Creasman, W. T. *et al.* Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* **95**(Suppl 1), S105–143, [https://doi.org/10.1016/S0020-7292\(06\)60031-3](https://doi.org/10.1016/S0020-7292(06)60031-3) (2006).
73. Odicino, F., Tisi, G. C., Miscioscia, R. & Pasinetti, B. Controversies in the Surgery of Endometrial Cancer. In *Cancer of the Uterine Endometrium-Advances and Controversies*. InTech (2012).
74. Sartori, E. *et al.* Clinical behavior of 203 stage II endometrial cancer cases: the impact of primary surgical approach and of adjuvant radiation therapy. *Int J Gynecol Cancer* **11**, 430–437 (2001).
75. Gadducci, A., Cosio, S. & Genazzani, A. R. *Treatment Planning in Endometrial Cancer*. *Cancer Therapy*. **1**, 373–391 (2003).
76. Seagle, B. L. *et al.* Survival after pelvic exenteration for uterine malignancy: A National Cancer Data Base study. *Gynecol Oncol* **143**, 472–478, <https://doi.org/10.1016/j.ygyno.2016.10.018> (2016).
77. Lachance, J. A., Stukenborg, G. J., Schneider, B. F., Rice, L. W. & Jazaeri, A. A. A cost-effective analysis of adjuvant therapies for the treatment of stage I endometrial adenocarcinoma. *Gynecol Oncol* **108**, 77–83, <https://doi.org/10.1016/j.ygyno.2007.08.072> (2008).

Acknowledgements

The project described was partially supported by the National Institutes of Health, Grant 1TL1TR001443 of CTSA funding (KT, VT). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Author Contributions

R.O., V.T., Q.N. and K.M. provided data analysis or analysis oversight. K.M. provided guidance on the statistics of the data analysis. R.O., V.T., and Q.N. organized, compiled, and wrote the manuscript. J.C., B.C., E.C., C.K., S.L., K.M., A.M., J.M., J.P., A.S., K.T. and A.W. provided contributions for results interpretation, manuscript literature review, discussion, and critical manuscript review and approval. Figures were prepared by V.T.

Additional Information

Supplementary information accompanies this paper at <https://doi.org/10.1038/s41598-018-23403-5>.

Competing Interests: The authors declare no competing interests.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2018